DOI: 10.1002/ncp.10763

Clinical Research

Protein requirements for critically ill ventilator-dependent patients with COVID-19

Christopher T. Buckley PharmD[1] | **Nivedita Prasanna MD**[2] | **Abby L. Mays RD**[3] | **Jeanette M. Tinsley RD**[3] | **Roland N. Dickerson PharmD**[4]

[1] Department of Pharmacy Practice, Union University, College of Pharmacy, Jackson, Tennessee, USA

[2] Department of Critical Care Medicine, Jackson-Madison County General Hospital, Jackson, Tennessee, USA

[3] Department of Nutrition, Jackson-Madison County General Hospital, Jackson, Tennessee, USA

[4] Department of Pharmacy and Translational Science, University of Tennessee Health Science Center, Memphis, Tennessee, USA

Correspondence
Christopher T. Buckley, PharmD, Department of Pharmacy Practice, Union University, College of Pharmacy, 1050 Union University Drive, Jackson, TN 38305, USA.
Email: cbuckley@uu.edu

Background: Recent studies indicate critically ill patients with coronavirus disease 2019 (COVID-19) are hypermetabolic; however, protein requirements in critically ill COVID-19 patients are unknown. Our intent was to evaluate the nitrogen accretion response to varying protein intakes for critically ill ventilator-dependent patients with COVID-19.

Methods: Adult patients (age ≥ 18 years) with COVID-19, admitted to the intensive care unit (ICU) and who required mechanical ventilation were retrospectively evaluated. Patients received continuous enteral nutrition (EN), including supplemental protein boluses, and had a 24-h urine collection for determination of nitrogen balance (NBAL). Data are expressed as mean ± SD with a *P*-value < .05 as significant.

Results: Twenty-two patients provided 29 NBAL determinations. Protein intake from EN and protein supplements was 0.9 ± 0.7 g/kg/day at the time of the NBAL with an NBAL of –12.1 ± 10.9 g/day at 7 ± 4 days in the ICU. Combined caloric intake from EN and propofol at the time of the NBAL was 12 ± 8 kcal/kg/day. Nitrogen equilibrium (NBAL of –4 g/day or better) occurred in five patients. Patients achieving nitrogen equilibrium received more protein than those with a negative NBAL (1.2 ± 0.4 g/kg/day vs 0.8 ± 0.8 g/kg/day, $P = .046$). The linear regression for NBAL in response to graded increases in protein intake was as follows: NBAL = 8.5 × protein intake (g/kg/day) – 18.8 ($r = 0.450$, $P < .001$).

Conclusion: Critically ill ventilator-dependent patients with COVID-19 exhibit significant variability in nitrogen accretion response to increases in protein intake and often have a markedly negative NBAL.

KEYWORDS
COVID-19, critical illness, enteral nutrition, nitrogen balance, nutrition support, protein

INTRODUCTION

Management of critically ill patients with coronavirus disease 2019 (COVID-19) has exposed many healthcare challenges. Because enteral nutrition (EN) is beneficial for blunting the inflammatory catabolic state, supporting immune function, and maintenance of gut barrier integrity in ventilator-dependent, critically ill patients,[1] it is presumed to be useful for critically patients with COVID-19. However, definition of an optimal macronutrient regimen for these patients is still largely unknown.[2] Patients with severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) exhibit a marked hyperdynamic state presumably due to a cytokine storm and exaggerated production of other inflammatory mediators.[1] Recent studies suggest critically ill patients with SARS-CoV-2 exhibit marked hypermetabolism which may be sustained for weeks.[3–5] Disease states with hypermetabolism are also often associated with increased net protein catabolism.[6,7] However, there is a paucity of data evaluating protein requirements for these patients. The primary objective of this study was to evaluate protein requirements for critically ill ventilator-dependent patients with SARS-CoV-2 disease.

METHODS

This retrospective observational study evaluated patients admitted to the intensive care unit (ICU) with SARS-CoV-2 disease. Patients were included if they were ≥18 years old, admitted to the hospital from October 1, 2020, to January 31, 2021, and required mechanical ventilation within 7 days of admission. Patients were given EN and had a 24-h urine collection for determination of nitrogen balance (NBAL) and creatinine clearance. This study was approved by the Institutional Review Board of the University and Hospital. The requirement for informed consent was waived.

Patient demographic information was collected, which included age, weight, sex, race, and pertinent comorbidities. Severity of illness was evaluated using the Sequential Organ Failure Assessment (SOFA)[8] score, Acute Physiology and Chronic Health Evaluation II (APACHE II)[9] score, and modified Nutrition Risk in Critically Ill (mNUTRIC)[10] score, without interleukin-6, on the day of the 24-h urine collection. Other relevant collected data included serum C-reactive protein, triglycerides, minute ventilation, ventilator days, hospital mortality, hospital length of stay, and ICU length of stay. Pertinent pharmacotherapy such as dexamethasone, vasopressors, propofol, prokinetic pharmacotherapy, and neuromuscular blockers were also recorded.

All patients received continuous EN via a nasogastric or orogastric feeding tube. Patients were prescribed supplemental protein doses, when indicated, to meet target caloric and protein goals. Admission body weight was used to determine nutrition goals, and body mass index (BMI) was used to identify the presence of obesity. A patient with a BMI of 30 kg/m^2 or greater was defined as obese. Target caloric and protein intakes for the first week of ICU admission were 15–20 kcal/kg and 1.2–2 g/kg/day, respectively, for nonobese patients.[1] For patients with obesity, target caloric, and protein goals were 22–25 kcal/kg and 2–2.5 g/kg/day based on ideal body weight, respectively.[11,12] This hypocaloric strategy was chosen to reduce nutrition-related carbon dioxide production[13] as ventilator-dependent patients with SARS-CoV-2 often undergo permissive hypercapnia to avoid ventilation-induced lung injury syndrome. Protein and caloric intakes from the EN, including calories from intravenous propofol therapy, were recorded on the day of the NBAL determination. Energy intakes were decreased, and protein intakes were maintained by a reduction in the EN feeding rate and administration of liquid protein boluses for those receiving additional caloric intake from propofol therapy.[14]

A 24-h urine collection for the determination of NBAL and creatinine clearance was conducted as part of routine clinical practice during their ICU stay. Urine was collected via an indwelling urinary catheter. The urine collection was evaluated for completeness of the collection by one of the investigators (CTB) at the time of the measurement including an interview of the patient's nurse regarding any potential disposal of the urine collection. Urine collections deemed inaccurate were not used for clinical purposes nor in this analysis. Nursing staff transferred the urine from indwelling catheters to urine collection containers while wearing appropriate personal protective equipment. Urine collection containers were transported to the hospital laboratory in biohazard bags and assayed for urea nitrogen and creatinine. NBAL was estimated by the following equation[6,15]:

$$\mathrm{NBAL(g/day)} = \mathrm{Nitrogenintake(g/day)} - \mathrm{Urinaryureanitrogen(g/day)} \div 0.85 - 2\mathrm{(g/day)}.$$

If a change in serum urea nitrogen concentration by >2 mg/dl occurred during the balance study, body urea nitrogen appearance was estimated and included in the NBAL determination.[6] Two grams of nitrogen were presumed for integumentary and insensible nitrogen losses.[6,16] Nitrogen equilibrium was defined as a NBAL of −4 g/day to +4 g/day, with a positive NBAL defined as >4 g/day and a negative NBAL defined as worse than −4 g/day. The measured creatinine clearance was calculated as: = [urine creatinine excretion (mg/day) ÷ (serum creatinine

[mg/dl] × 1440 [min/day])] × 100 (ml/dl). Estimated creatinine clearance was calculated using the Cockcroft-Gault equations.[17] Both estimated and measured creatinine clearances were then normalized to a body surface area of 1.73 m^2 using the method of Mosteller.[18]

Continuous data were expressed as mean ± SD. Data analysis was conducted using SigmaPlot for Windows version 11.1 (Systat Software Inc, San Jose, CA). A *P*-value <.05 was established as statistically significant. Differences between independent groups were evaluated by the Student *t*-test or Wilcoxon rank sum test depending on normality of the data. Nominal data between groups were evaluated by the Fisher exact test. The difference between paired measured and predicted creatinine clearance measurements was evaluated by the Wilcoxon signed rank test. Goodness of fit of the linear model between NBAL and protein intake (g/kg/day) was assessed by Pearson correlation analysis.

RESULTS

Twenty-two patients admitted to the ICU with SARS-CoV-2 requiring EN therapy were enrolled into the study, with all patients (n = 22) contributing at least one NBAL determination and seven contributing two measurements for a total 29 NBAL determinations. Patient characteristics revealed an older population with only two patients <50 years of age and were predominantly White (73%) and male (64%). Common past medical histories included diabetes (32%), obesity (45%), and hyperlipidemia (68%).

All patients required mechanical ventilation during their hospitalization. Patients experienced a systemic inflammatory hyperdynamic state as evidenced by an elevated C-reactive protein concentration and high minute ventilation volume. A high rate of hospital mortality (about two-thirds of the studied population) was observed. Patients experienced a prolonged ICU and hospital length of stay. On the day of NBAL, patients exhibited a high level of severity of illness as evidenced by an average APACHE II score of 23, SOFA score of 8, and an mNUTRIC score of 6 (Table 1).Patients received intravenous dexamethasone during most of the NBAL determinations (n = 20), with the majority (n = 16) receiving 6 mg daily. Patients received vasopressor (norepinephrine) therapy in about a third of the NBAL determinations, whereas 10% and 7% of the observations were during pharmacologic neuromuscular blockade and prone positioning, respectively. None of the patients received prokinetic pharmacotherapy[19] at the time of the NBAL determination. Demographic data are given in Table 1.

Average target total caloric intake (from EN and propofol) was ~1450–1650 kcal/day and ~1350–1800 kcal/day for

TABLE 1 Patient characteristics, laboratory values, and clinical outcomes

Variable	Results
N	22
Age, years	66 ± 14
Sex, n (%)	
Female	8 (36)
Male	14 (64)
Race, n (%)	
White	16 (73)
African American	6 (27)
Height, cm	175 ± 9
Admission weight, kg	92 ± 19
BMI, kg/m^2	30 ± 6
BSA, m^2	2.1 ± 0.2
Concurrent medical conditions, n (%)	
Pancreatitis	1 (4)
Diabetes mellitus	7 (32)
Obesity	10 (45)
Hyperlipidemia	15 (68)
Chronic kidney disease	2 (9)
Cirrhosis	2 (9)
APACHE II score	23 ± 7
SOFA score	8 ± 3
mNUTRIC score	6 ± 2
GCS score	6.8 ± 2.9
Required mechanical ventilation, n (%)	22 (100)
Minute ventilation, L/min	11.4 ± 2.7
pH	7.41 ± 0.07
PaO_2, mm Hg	88 ± 51
FiO_2, %	69 ± 24
Prone position during NBAL, n (%)	2 (7)[a]
Heart rate, beats per minute	95 ± 23
Temperature, °C	37.4 ± 0.8
C-reactive protein, mg/dl	11.7 ± 10.3
Triglycerides, mg/dl	254 ± 212
WBC, cells per millimeter cubed	12.1 ± 6.7
Dexamethasone, n (%)	23 (79)[a]
Vasopressors, n (%)	9 (31)[a]
Neuromuscular blockers, n (%)	3 (10)[a]
Hospital mortality, n (%)	15 (68)
Ventilator days, days	22 ± 30
ICU LOS, days	23 ± 29
Hospital LOS, days	25 ± 29

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; BSA, body surface area; FiO_2, fraction of inspired oxygen; GCS, Glasgow Coma Scale; ICU, intensive care unit; LOS, length of stay; mNUTRIC, modified Nutrition Risk in Critically Ill; n, number of patients; NBAL, nitrogen balance; PaO_2, arterial oxygen concentration; SOFA, Sequential Organ Failure Assessment; WBC, white blood cell count.
[a]During the NBAL out of 29 total NBAL determinations.

TABLE 2 Nutrition intake, NBAL, and creatinine clearance

Variable	Results (N = 29)
Caloric intake from EN, kcal/day	885 ± 648
Caloric intake from EN, kcal/kg/day	10 ± 8
Propofol, kcal/day	193 ± 285
Propofol, kcal/kg/day	2 ± 3
Total caloric intake[a], kcal/day	1078 ± 741
Total caloric intake[a], kcal/kg/day	12 ± 8
Protein received, g/day	77 ± 59
Protein received, g/kg/day	0.9 ± 0.7
Urine urea nitrogen, g/day	19.4 ± 10.8
Estimated total nitrogen excretion, g/day	24.4 ± 12.0
NBAL, g/day	–12.1 ± 10.9
Serum creatinine, mg/dl	1.1 ± 0.5
Measured creatinine clearance, ml/min/1.73m^2	58 ± 42
Cockcroft-Gault creatinine clearance, ml/min/1.73m^2	95 ± 67*
24-h urine output, ml	1645 ± 928
ICU day of NBAL, days	7 ± 4

Abbreviations: EN, enteral nutrition; ICU, intensive care unit; N, number of observations; NBAL, nitrogen balance.

[a]Combined intake from EN and propofol.

*$P < .001$ compared with measured creatinine clearance

the obese and nonobese patients, respectively. Average target protein intake was 130–165 g/day and 105–175 g/day for the obese and nonobese patients, respectively. Total caloric intake (propofol and EN) and protein intake during the NBAL determination were 1170 ± 741 kcal/day and 1012 ± 755 kcal/day ($P = .581$) and 77 ± 49 g/day and 77 ± 67 g/day ($P = .929$) for the obese and nonobese patients, respectively.

Nutrition intakes from the EN and propofol during the NBAL determinations for all patients are given in Table 2. Nine patients received a continuous propofol infusion, providing an average of 6 ± 3 kcal/kg/day (range, 3–10 kcal/kg/day) for those who received propofol. The NBAL response to increasing doses of protein was highly variable with most patients experiencing a substantial negative NBAL (Figure 1). NBAL among all protein intakes averaged –12.1 g/day (Table 2) with one patient experiencing an NBAL of nearly –40 g/day while receiving 1.4 g/kg/day of protein (Figure 1). Serum urea nitrogen concentration during the NBAL determination did not significantly increase (from 51 ± 23 mg/dl to 54 ± 27 mg/dl, $P = .120$); however, an adjustment in NBAL was necessary for 17 determinations (59% of measurements). Administration of dexamethasone did not significantly worsen NBAL when compared with those without dexamethasone therapy (–11.1 ± 12.0 g/day vs –15.8 ± 4.1 g/day, respectively; $P = .352$). These results were not attributable to a difference in protein intake during the NBAL study (0.8 ± 0.6 g/kg/day vs 0.7 ± 0.7 g/kg/day for those measurements with and without dexamethasone therapy, respectively; $P = .667$). Mean serum creatinine concentration during the NBAL determination was 1.1 ± 0.5 mg/dl; three patients experienced a serum creatinine concentration >1.5 mg/dl. Measured creatinine clearance was lower than predicted by the Cockcroft-Gault equations ($P < .001$, Table 2).

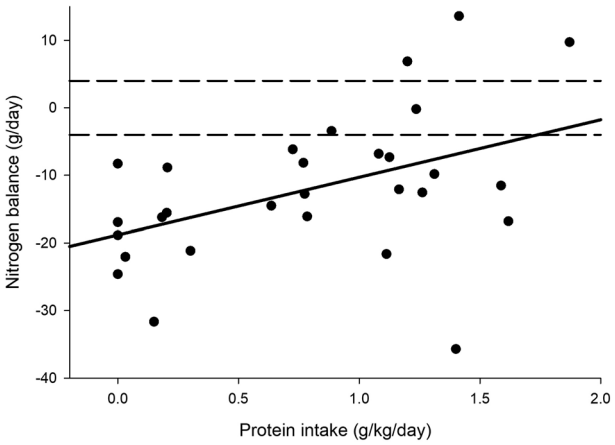

FIGURE 1 Influence of graded increases in protein intake upon nitrogen balance. Each nitrogen balance-protein intake data point is represented by the closed circles. The dashed lines represent the upper and lower limits of nitrogen equilibrium as defined as a nitrogen balance of -4 g/day to +4 g/day. The solid line depicts the linear relationship between nitrogen balance and protein intake. The linear regression is expressed as: nitrogen balance (g/day) = 8.51 × protein received (g/kg/day) – 18.8; $r = 0.450$; $P < .001$

TABLE 3 Comparison of groups by achievement of nitrogen equilibrium

Variable	Achieved nitrogen equilibrium	Negative NBAL	*P*-value
Number of observations	5	24	–
Number of patients	5	17	–
Age, years	67 ± 22	65 ± 13	.469
Weight, kg	95 ± 15	93 ± 19	.751
BMI, kg/m^2	30 ± 3	30 ± 7	.640
APACHE II score	23 ± 6	23 ± 7	.961
SOFA score	9.2 ± 2.8	7.9 ± 2.9	.380
mNUTRIC score	6 ± 2	6 ± 2	.517
Serum creatinine, mg/dl	0.8 ± 0.3	1.1 ± 0.5	.507
Serum urea nitrogen, mg/dl	43 ± 17	57 ± 29	.506
Energy intake from EN, kcal/day	1450 ± 389	767 ± 633	.029
Energy intake from EN, kcal/kg/day	15 ± 2	9 ± 8	.046
Energy intake from propofol, kcal/day	212 ± 202	189 ± 303	.728
Energy intake from propofol, kcal/kg/day	2 ± 2	2 ± 3	.776
Total energy intake, kcal/day	1662 ± 534	956 ± 727	.051
Total energy intake, kcal/kg/day	17 ± 3	11 ± 9	.111
Protein intake, g/day	117 ± 29	69 ± 61	.078
Protein intake, g/kg/day	1.2 ± 0.4	0.8 ± 0.8	.046
NBAL, g/day	5.3 ± 7.0	−15.7 ± 7.6	.001
ICU day of NBAL, days	7 ± 3	7 ± 4	.521
Ventilator days	35 ± 43	16 ± 13	.468
ICU LOS, days	38 ± 42	17 ± 12	.348
Hospital LOS, days	38 ± 42	20 ± 13	.551
Hospital mortality, n (%)	4 (80)	11 (65)	1.000

Note: The en dashes (–) denote that there are no data.

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; EN, enteral nutrition; ICU, intensive care unit; LOS, length of stay; mNUTRIC, modified Nutrition Risk in Critically Ill; NBAL, nitrogen balance; SOFA, Sequential Organ Failure Assessment.

Nitrogen equilibrium or a positive NBAL was achieved in only 5 out of 29 observations. There was no difference in age or severity of illness as assessed by APACHE II score, SOFA score, or mNUTRIC score between those who achieved nitrogen equilibrium or a positive NBAL vs those with a negative NBAL (Table 3). Timing of the NBAL determination was also similar for both groups at an average of 7 days postadmission to the ICU. Those who achieved nitrogen equilibrium or a positive NBAL received significantly more protein than those who were in negative NBAL with an average protein intake of 1.2 g/kg/day vs 0.8 g/kg/day ($P = .046$, respectively; Table 3). Total combined caloric intake from EN and propofol also tended to be greater for those who achieved nitrogen equilibrium or a positive NBAL, but the difference did not achieve statistical significance (Table 3). Application of a linear regression model for NBAL across all protein intakes indicated that 1.5 g/kg/day of protein would be required to achieve nitrogen equilibrium as defined by an NBAL of −4 g/day or better (Figure 1). Clinical outcomes were not different between in those who achieved nitrogen equilibrium or positive NBAL vs those exhibiting a negative NBAL (Table 3); however, the number of patients in this study is underpowered to detect clinical outcome differences.

DISCUSSION

Our study indicates that patients who are critically ill and ventilator-dependent with severe COVID-19 disease exhibit exaggerated and variable levels of net protein catabolism similar to that of critically ill patients with multiple traumatic injuries.[6] Despite the marked inflammatory and hyperdynamic state, patients did not experience augmented renal clearance as previously observed in older critically ill patients who required nutrition support therapy.[20–22] These observations also reflect that the renal functional reserve response for

patients with COVID-19 may have been dampened when compared with other hypermetabolic-hypercatabolic conditions encountered in current clinical practice.[6] From the regression analysis model (Figure 1), the nitrogen accretion response to increases in protein intake was highly variable of which many exhibited a marked negative NBAL. These data indicate that individualization of protein intake for critically ill ventilator-dependent patients with SARS-CoV-2 is warranted.

Because of the lack of data regarding protein requirements for patients with COVID-19, both the American Society for Parenteral and Enteral Nutrition (ASPEN) and European Society for Clinical Nutrition and Metabolism (ESPEN), formerly the European Society for Parenteral and Enteral Nutrition, recommend protein intakes equivalent to their previous guideline recommendations for critically ill patients.[23,24] For critically ill patients with COVID-19, ASPEN recommends a protein intake of 1.2–2 g/kg/day in patients with a normal body weight and 2–2.5 g/kg/day based on ideal body weight for patients with obesity.[1] ESPEN recommends 1.3 g/kg/day [25] and >1 g/kg/day adjusted body weight for those with obesity.

Adjusted body weight was calculated in the ESPEN guidelines by: ideal body weight + ([actual weight – ideal body weight] × 0.25)[26]

Recent indirect calorimetry studies demonstrate many critically ill patients with COVID-19 exhibit hypermetabolism.[3–5] One study indicated that hypermetabolism (measured energy expenditure > 110% of predicted) occurred in two-thirds of their patients.[3] They also observed that the hypermetabolism persisted beyond 1 week post–ICU admission.[3] Others have suggested that the hypermetabolism may be sustained for 3 weeks post–ICU admission.[4] Disease conditions exhibiting hypermetabolism are generally associated with increased net protein catabolism.[6,7] Our data indicate that critically ill patients with SARS-CoV-2 exhibit marked net protein catabolism as assessed by NBAL studies. The average NBAL was –12 g/day at a mean protein intake of 0.9 g/kg/day with one patient experiencing an NBAL of nearly –40 g/day while receiving 1.4 g/kg/day of protein. The linear regression analysis examining NBAL at graded doses of protein suggests a marked net catabolic state with an NBAL of about –19 g/day when no exogenous protein is provided (Figure 1). This level of net protein catabolism reflects that observed with critically ill patients with multiple traumatic injuries[6] who are considered to be among the most catabolic populations encountered in clinical practice.[6,23] This observation is particularly poignant as our population was older with potential anabolic resistance to protein intake,[20,22] suffered chronic diseases, and likely had less muscle mass than the younger critically ill patients with multiple traumatic injuries counterparts.[20]

At the time of writing this manuscript, we are aware of only two other published works (a preprint manuscript and a letter to the editor) whereby NBAL determinations were evaluated for patients with COVID-19.[3,27] Lakenman and associates[3] evaluated the nitrogen accretion response during the acute phase postadmission to the ICU (≤7 days) and during late phase (>7 days). Their data indicated net protein catabolism was not pronounced until the late phase. Median NBAL was –1.5 g/day (interquartile range [IQR] of –4.5 to 5.1 g/day) while receiving 1.0 ± 0.4 g/kg/day of protein during the early phase compared with –10.1 (IQR, –1.9 to –16.2) while receiving 1.3 ± 0.3 g/kg/day of protein during the late phase. The second study[27] indicated a median NBAL of –8.7 g/day (IQR, –3.6 to –12.2 g/day) while receiving 1.3 g/kg/day (IQR, 1.0–1.6 g/kg/day) at day 7 postadmission to the ICU. These results were comparable with our findings; however, our population exhibited greater variability in urinary nitrogen loss. Additionally, it was difficult to compare populations with our study as both studies did not provide sufficient details regarding clinical outcomes, severity of illness scores, urea nitrogen appearance, renal function, pharmacotherapy known to potentially influence net protein catabolism, or EN tolerance for a more in-depth comparative analysis.

About 80% of the NBAL determinations were conducted when patients received dexamethasone therapy. Dexamethasone, at an intravenous dose of 6 mg daily for up to 10 days or at discharge from the ICU if sooner, decreases 28-day mortality for critically ill patients with COVID-19 who require invasive mechanical ventilation or oxygen support.[28] Corticosteroids, such as dexamethasone, can increase muscle catabolism and worsen NBAL. Methylprednisolone (given at an equivalent dose to 16 mg/day of dexamethasone) increases urinary nitrogen excretion by 30%–50% in patients with head injuries.[29] High-dose dexamethasone therapy (16 mg or 40 mg daily) has been previously reported to result in a disproportionate increase in the caloric contribution of protein oxidation to energy expenditure in patients with head injuries from an anticipated ~20% with trauma, sepsis, and critical illness[30] to ~25%–30%.[31,32] No detrimental effect upon NBAL from these lower doses of dexamethasone occurred when comparing measurements taken during and without dexamethasone therapy; however, the number of observations when not receiving dexamethasone therapy was limited and requires further study.

Despite the hyperdynamic and catabolic features associated with COVID-19–associated critical illness, patients did not demonstrate evidence of augmented renal clearance whereby measured creatinine clearance is substantially greater than estimated based on predictive formulas that employ a serum creatinine concentration. Augmented renal clearance has been demonstrated for

other critically ill populations as trauma, sepsis, and thermal injury,[21] even in older patients.[6,21,22] Despite only three patients having a serum creatinine concentration >1.5 mg/dl, measured creatinine clearance was lower than predicted and serum urea nitrogen concentrations were also higher than anticipated. SARS-CoV-2 is often associated with multiple organ dysfunction syndrome. It has been reported that the development of acute kidney injury is associated with high mortality for patients with severe COVID-19 disease.[33] COVID-19–induced renal impairment prior to overt acute kidney injury may be insidious, particularly when renal function is assessed by serum creatinine concentration alone. Autopsy data demonstrated significant renal microvascular damage in patients who died from COVID-19 without clinical detection of renal dysfunction via serum creatinine concentrations in 9 out of 18 patients.[34] Serum urea nitrogen concentrations for the patients in our study were higher than empirically anticipated based on serum creatinine concentrations and the modest protein intakes given to these patients. In the absence of dehydration, gastrointestinal bleeding, acute kidney injury, or excessive protein intake, an elevated serum urea nitrogen to creatinine ratio has been proposed as a biochemical signature for substantial muscle catabolism.[35] An elevated serum urea nitrogen to creatinine ratio has also been associated with more severe disease and higher mortality for patients with COVID-19.[36]

Cantaluppi and coauthors have suggested that the high mortality observed in comorbid and elderly patients with severe COVID-19 is related to a reduced renal functional reserve.[37] Renal functional reserve is the ability to increase glomerular filtration rate in response to critical illness and protein intake.[38] Elevated serum urea nitrogen concentrations with respect to serum creatinine concentration along with a measured creatinine clearance lower than anticipated by predictive equations for patients in our study provides indirect evidence of dampening of the renal functional reserve response to critical illness. Further research regarding the influence of COVID-19 upon renal functional reserve and the nature of COVID-19–induced renal impairment requires more study.

This study has limitations. This was a retrospective, single-center study that evaluated a small number of patients who only received EN, which limits its generalizability to other institutions. NBAL has historically been used as a surrogate marker for estimating protein requirements; however, it is unclear how it correlates with clinical outcomes. Steady state NBAL measurements were not possible because of interruptions in enteral feeding and day-to-day variability in the patients' clinical status. Additionally, it is difficult to conduct in clinical practice and only reflects the net difference between intake and output. It does not reveal information regarding nitrogen synthesis or catabolism. It would have been helpful to have multiple serial NBAL determinations per patient to examine overall protein balance, individual responses to varying protein intakes, quantification of the duration of net protein catabolism, and to ascertain if increased protein delivery results in improved nitrogen accretion. Most patients did not achieve intended caloric or protein goals. Delivery of EN is not without challenges, as critically ill patients with COVID-19 may have associated gastrointestinal symptoms, acute respiratory distress syndrome with refractory hypoxemia requiring utilization of prone positioning, hypotension, or shock requiring the use of vasopressors, and the progression to multisystem organ failure. One study reports high incidences of hypomotility with 46% of patients developing gastric feeding intolerance and 56% of patients with a clinical or radiographic diagnosis of ileus.[39]

CONCLUSION

Patients who are critically ill and ventilator-dependent with severe COVID-19 disease often exhibit a substantially negative NBAL. Despite the marked inflammatory and hyperdynamic state, patients did not experience augmented renal clearance. The linear regression analysis suggested 1.5 g/kg/day of protein is required to achieve nitrogen equilibrium; however, the nitrogen accretion response to increases in protein intake was highly variable, which indicates that individualization of protein intake for critically ill ventilator-dependent patients with SARS-CoV-2 is warranted.

ACKNOWLEDGMENTS

The authors would like to acknowledge Alexandria Hines, PharmD and the neurological intensive care unit nursing staff for their contributions to this study.

FUNDING INFORMATION

None declared.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Christopher T. Buckley and Roland N. Dickerson contributed to the conception and design of the research; Christopher T. Buckley, Abby L. Mays, and Jeanette M. Tinsley contributed to the acquisition of the data; Roland N. Dickerson contributed to the analysis of the data; Christopher T. Buckley, Nivedita Prasanna, Abby L. Mays, Jeanette M. Tinsley, and Roland N. Dickerson contributed to interpretation of the data; and Christopher T. Buckley

and Roland N. Dickerson drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

ORCID

Christopher T. Buckley PharmD https://orcid.org/0000-0003-2398-2273
Roland N. Dickerson PharmD https://orcid.org/0000-0002-2086-6317

REFERENCES

1. Martindale R, Patel JJ, Taylor B, Arabi YM, Warren M, McClave SA. Nutrition therapy in critically ill patients with coronavirus disease 2019. *JPEN J Parenter Enteral Nutr*. 2020;44(7):1174-1184.
2. Mechanick JI, Carbone S, Dickerson RN, et al. Clinical nutrition research and the COVID-19 pandemic: a scoping review of the ASPEN COVID-19 task force on nutrition research. *JPEN J Parenter Enteral Nutr*. 2021;45(1):13-31.
3. Lakenman PLM, van der Hoven B, Schuijs JM, et al. Energy expenditure and feeding practices and tolerance during the acute and late phase of critically ill COVID-19 patients. *Clin Nutr ESPEN*. 2021;43:383-389.
4. Whittle J, Molinger J, MacLeod D, Haines K, Wischmeyer PE; LEEP-COVID Study Group. Persistent hypermetabolism and longitudinal energy expenditure in critically ill patients with COVID-19. *Crit Care*. 2020;24(1):581.
5. Yu PJ, Cassiere H, DeRosa S, Bocchieri K, Yar S, Hartman A. Hypermetabolism and coronavirus disease 2019. *JPEN J Parenter Enteral Nutr*. 2020;44(7):1234-1236.
6. Dickerson RN, Pitts SL, Maish GO, et al. A reappraisal of nitrogen requirements for patients with critical illness and trauma. *J Trauma Acute Care Surg*. 2012;73(3):549-557.
7. Hart DW, Wolf SE, Mlcak R, et al. Persistence of muscle catabolism after severe burn. *Surgery*. 2000;128(2):312-319.
8. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;22(7):707-710.
9. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985;13(10):818-829.
10. Heyland DK, Dhaliwal R, Jiang X, Day AG. Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool. *Crit Care*. 2011;15(6):R268.
11. Choban P, Dickerson R, Malone A, et al. A.S.P.E.N. Clinical guidelines: nutrition support of hospitalized adult patients with obesity. *JPEN J Parenter Enteral Nutr*. 2013;37(6):714-744.
12. Choban PS, Dickerson RN. Morbid obesity and nutrition support: is bigger different?. *Nutr Clin Pract*. 2005;20(4):480-487.
13. Talpers SS, Romberger DJ, Bunce SB, Pingleton SK. Nutritionally associated increased carbon dioxide production. Excess total calories vs high proportion of carbohydrate calories. *Chest*. 1992;102(2):551-555.
14. Buckley CT, Van Matre ET, Fischer PE, Minard G, Dickerson RN. Improvement in protein delivery for critically ill patients requiring high-dose propofol therapy and enteral nutrition. *Nutr Clin Pract*. 2021;36(1):212-218.
15. Dickerson RN, Tidwell AC, Minard G, Croce MA, Brown RO. Predicting total urinary nitrogen excretion from urinary urea nitrogen excretion in multiple-trauma patients receiving specialized nutritional support. *Nutrition*. 2005;21(3):332-338.
16. Shaw-Delanty SN, Elwyn DH, Jeejeebhoy KN, et al. Components of nitrogen excretion in hospitalised adult patients on intravenous diets. *Clin Nutr*. 1987;6(4):6257-6266.
17. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31-41.
18. Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med*. 1987;317(17):1098.
19. Dickerson RN, Mitchell JN, Morgan LM, et al. Disparate response to metoclopramide therapy for gastric feeding intolerance in trauma patients with and without traumatic brain injury. *JPEN J Parenter Enteral Nutr*. 2009;33(6):646-655.
20. Dickerson RN. Nitrogen balance and protein requirements for critically ill older patients. *Nutrients*. 2016;8(4):226.
21. Dickerson RN, Crawford CN, Tsiu MK, et al. Augmented renal clearance following traumatic injury in critically ill patients requiring nutrition therapy. *Nutrients*. 2021;13(5):1681.
22. Dickerson RN, Maish GO III, Croce MA, Minard G, Brown RO. Influence of aging on nitrogen accretion during critical illness. *JPEN J Parenter Enteral Nutr*. 2015;39(3):282-290.
23. McClave SA, Taylor BE, Martindale RG, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition. *JPEN J Parenter Enteral Nutr*. 2016;40(2):159-211.
24. Singer P, Blaser AR, Berger MM, et al. ESPEN guideline on clinical nutrition in the intensive care unit. *Clin Nutr*. 2019;38(1):48-79.
25. Barazzoni R, Bischoff SC, Breda J, et al. ESPEN expert statements and practical guidance for nutritional management of individuals with SARS-CoV-2 infection. *Clin Nutr*. 2020;39(6):1631-1638.
26. Barazzoni R, Bischoff SC, Busetto L, et al. Nutritional management of individuals with obesity and COVID-19: ESPEN expert statements and practical guidance. *Clin Nutr*. Published online May 11, 2021. doi: 10.1016/j.clnu.2021.05.006
27. Formenti P, Bichi F, Castagna V, Pozzi T, Chiumello D. Nutrition support in patients with acute respiratory distress syndrome COVID-19. *Nutr Clin Pract*. 2021;36(2):500-501.
28. Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med*. 2021;384(8):693-704.
29. Deutschman CS, Konstantinides FN, Raup S, Cerra FB. Physiological and metabolic response to isolated closed-head injury. Part 2: effects of steroids on metabolism. Potentiation of protein wasting and abnormalities of substrate utilization. *J Neurosurg*. 1987;66(3):388-395.
30. Duke JH Jr, Jorgensen SB, Broell JR, Long CL, Kinney JM. Contribution of protein to caloric expenditure following injury. *Surgery*. 1970;68(1):168-174.
31. Clifton GL, Robertson CS, Grossman RG, Hodge S, Foltz R, Garza C. The metabolic response to severe head injury. *J Neurosurg*. 1984;60(4):687-696.

32. Dickerson RN, Guenter PA, Gennarelli TA, Dempsey DT, Mullen JL. Increased contribution of protein oxidation to energy expenditure in head-injured patients. *J Am Coll Nutr*. 1990;9(1):86-88.
33. Nadim MK, Forni LG, Mehta RL, et al. COVID-19-associated acute kidney injury: consensus report of the 25th acute disease quality initiative (ADQI) workgroup. *Nat Rev Nephrol*. 2020;16(12):747-764.
34. Su H, Yang M, Wan C, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int*. 2020;98(1):219-227.
35. Haines RW, Zolfaghari P, Wan Y, Pearse RM, Puthucheary Z, Prowle JR. Elevated urea-to-creatinine ratio provides a biochemical signature of muscle catabolism and persistent critical illness after major trauma. *Intensive Care Med*. 2019;45(12):1718-1731.
36. Ok F, Erdogan O, Durmus E, Carkci S, Canik A. Predictive values of blood urea nitrogen/creatinine ratio and other routine blood parameters on disease severity and survival of COVID-19 patients. *J Med Virol*. 2021;93(2):786-793.
37. Cantaluppi V, Guglielmetti G, Dellepiane S, Marengo M, Mehta RL, Ronco C. A call to action to evaluate renal functional reserve in patients with COVID-19. *Am J Physiol Renal Physiol*. 2020;319(5):F792.
38. Fliser D, Zeier M, Nowack R, Ritz E. Renal functional reserve in healthy elderly subjects. *J Am Society of Nephrol*. 1993;3(7):1371-1377.
39. Kaafarani HMA, El Moheb M, Hwabejire JO, et al. Gastrointestinal complications in critically ill patients with COVID-19. *Ann Surg*. 2020;272(2):e61-e62.

How to cite this article: Buckley CT, Prasanna N, Mays AL, Tinsley JM, Dickerson RN Protein requirements for critically ill ventilator-dependent patients with COVID-19. *Nutr Clin Pract*. 2021;36:984–992. https://doi.org/10.1002/ncp.10763